Glad about SAD (PD)

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The Study of Antidepressants in Parkinson's Disease (SAD-PD)[1] is only the second multicenter double-blind treatment trial[2] for depression in Parkinson disease (PD), and the first in North America. Although there have been calls to sensitize neurologists to the problem of depression in PD, the result being that 20%–25% of patients with PD are taking an antidepressant at any given time, until recently there have been no data to suggest that it is a treatable problem,[3] a situation that still exists for depression in Alzheimer disease.[4] Given how common depression is in many neurodegenerative diseases and neurologic conditions, the paucity of research and positive treatment studies is alarming.

In SAD-PD, 115 subjects with PD, at 20 sites, with a range of depression diagnoses (more than half with major depressive disorder) and Hamilton Depression Rating Scale (HAM-D) scores >12 were randomized to 12 weeks of treatment with paroxetine, a selective serotonin reuptake inhibitor (SSRI; n = 42); venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI; n = 34); or placebo (n = 39). The primary outcome measure was change from baseline in HAM-D score. There was a range of secondary outcome measures.

The study convincingly met its primary endpoint, with support from secondary mood measures. Both paroxetine (mean dose = 24 mg/day) and venlafaxine (mean dose = 121 mg/day) were superior to placebo in reducing HAM-D score. It should be noted that the effects of venlafaxine at the mean dosage used in the study are primarily serotonergic, with the noradrenergic effects becoming more prominent at higher dosages. The most noteworthy secondary finding was that both active treatments were well tolerated, with high study completion rates and no significant change in Unified Parkinson's Disease Rating Scale motor scores compared with placebo treatment.

The treatment responses were robust in this study, particularly for paroxetine, with an average decrease in HAM-D scores of >50% in both active treatment groups and 60%–70% response rates for paroxetine based on the global change score. This suggests a substantial nonspecific treatment effect (nearly half of placebo patients met criteria for depression response, higher than reported for other recent controlled depression treatment studies in PD[5,6]). Given the more pronounced treatment effects with paroxetine, the possibility of treatment unmasking existed, although neither the subjects nor the investigators accurately guessed treatment assignments.

Most importantly, this study provides Level I evidence for an antidepressant treatment effect in patients without dementia with very mild PD, but there are important caveats. The mean Mini-Mental State Examination score was over 28.5 for each group, and few patients were Hoehn & Yahr stage 3 or worse in the "on" state. There are no data to indicate whether the SAD-PD results generalize to more severely affected patients with PD. Furthermore, despite the impressive results on the primary outcome variable, the number needed to treat to achieve remission of depression was 13 with paroxetine and 24 with venlafaxine, due to the high placebo response. Also, the findings for secondary outcome measures were mixed; there was evidence for a beneficial effect on sleep for both compounds, but no effect on anxiety, cognition, or overall health-related quality of life. Since anxiety and quality of life are closely associated with depression, this is surprising. Adverse event data were notable for an increase in both systolic and diastolic blood pressure, with hypertension reported as an adverse event in 10% of participants, with venlafaxine treatment.

There are other limitations as well. Most noteworthy was poor recruitment, to the extent that the final sample size was only half of projected enrollment, leading to some baseline between-group numerical imbalances. It is impossible to know if, or how, the results would have differed if the full sample size had been enrolled. With depression affecting

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somewhere between 30% and 50% of patients with PD, it is startling to note that 20 sites, with experienced investigators and large populations, recruited an average of 1 subject/site every 8 months. It is also worth noting that 2 other recent placebo-controlled depression treatment studies in PD have each enrolled approximately 50 participants at a single site over a similar, several-year period.[5,6] Given the importance of this study and ultimately its results, the truncated sample size represents missed opportunities, including the ability to adequately look at predictors of response (e.g., major depression vs nonmajor depression) and compare paroxetine with venlafaxine treatment. So one sad thing about SAD-PD is that the recruitment difficulties may give potential funders of similar neuropsychiatric treatment studies in PD pause before proceeding.

Limitations notwithstanding, we congratulate the SAD-PD investigators and participants for an important and well-done job. This study is important in that it gives clinicians and patients with PD scientific evidence to support the use of newer antidepressants, specifically SSRIs and SNRIs, for the treatment of depression in patients with PD without dementia. This includes patients with less severe depression as well. Such therapeutic trials can be undertaken without significant concern for worsening of parkinsonism or other side effects. Added to the results from other recent, controlled depression treatment studies in PD that have reported positive findings (for a dopamine agonist,[2] a tricyclic antidepressant,[5] and cognitive-behavioral therapy[7]), depression may be as treatable in PD as it is in the general population.

DISCLOSURE

Dr. Friedman serves on scientific advisory boards/as a consultant for Teva Pharmaceutical Industries Ltd., EMD Serono, Inc., ACADIA Pharmaceuticals, Genzyme Corporation, and Addex; has received funding for travel or speaker honoraria from Teva Pharmaceutical Industries Ltd., Boehringer Ingelheim, GlaxoSmithKline, United BioSource Corporation, and SCHWARZ PHARMA; serves as Editor-in-Chief for *Medicine & Health/Rhode Island* and on the editorial boards of *Parkinsonism & Related Disorders* and *Neurology Reviews*; receives publishing royalties for *Making the Connection Between Brain and Behavior: Coping with Parkinson's Disease* (Demos Health, 2007); serves on speakers' bureaus for Teva Pharmaceutical Industries Ltd., GlaxoSmithKline, Boehringer Ingelheim, and GE Healthcare; receives research support from Teva Pharmaceutical Industries Ltd., Boehringer Ingelheim, EMD Serono, Inc., Cephalon, Inc., ACADIA Pharmaceuticals, GE Healthcare, Schering-Plough Corp., the NIH, and the Michael J. Fox Foundation; and has served as a consultant in medico-legal cases. Dr. Weintraub serves on scientific advisory boards for Pfizer Inc, CHDI, Teva Pharmaceutical Industries Ltd, Avanir Pharmaceuticals, and Merck Serono; has received funding for travel or speaker honoraria from Novartis and Teva Pharmaceutical Industries Ltd.; serves on the editorial board of *Movement Disorders*; receives research support from Novartis, the NIH/NINDS, and the Michael J. Fox Foundation for Parkinson's Research; and receives licensing fees from the University of Pennsylvania for licensing of Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease.

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